Global shortages of BCG vaccine and tuberculous meningitis in children

The WHO estimates that 1 million children younger than 15 years developed tuberculosis globally in 2016, 58 000 of whom live in South Africa.[1] Vaccination with bacille Calmette-Guerín (BCG) has been an integral part of childhood immunisation programmes in countries with a high burden of tuberculosis for several decades. BCG traditionally has been considered to have limited efficacy in preventing tuberculosis disease in adults. However, BCG has consistently been shown to protect young children against miliary tuberculosis and tuberculous meningitis[2,3]—a devastating disease with high morbidity and mortality. Life-long disability is common in survivors,[4] resulting in substantial social, physical, and economic burden to children, families, and health services. WHO strongly recommends BCG vaccination be given to all neonates in settings with a high tuberculosis burden.[5]

Due to problems with vaccine production and limited supplier options in some countries, the global availability and procurement of BCG has been a challenge since 2013.[6] Concern was expressed in 2016 that this could lead to substantial increases in child mortality globally.[7] A mathematical model estimated that, globally, more than 100 000 deaths per birth cohort over the first 15 years of life could result from interrupted BCG vaccine supply.[8] To date, there have not been any empirical data to document the actual consequences of BCG shortages.

In the Western Cape province, South Africa, where BCG is routinely recommended at birth to all infants, BCG vaccine supply shortages were first experienced during 2015. Less than half the number of BCG vials were available for distribution in 2015 compared to the number of vials distributed annually in 2013 and 2014 (2013: 24 540 vials; 2014: 28 100 vials; 2015: 11 320 vials [personal communication: Sisanda Mtatambi, Biovac Institute]). Concerted efforts were made to reduce wastage of available stock, and the response of routine services resulted in only a 6% drop in reported BCG coverage (95% in 2014 to 89% in 2015 [personal communication: Sonia Botha, Western Cape Department of Health]).[9] However, some of these reported BCG doses included catch-up vaccinations for infants not receiving vaccinations at birth, and in high-burden tuberculosis settings, infants can be at risk of tuberculosis exposure before vaccination if not vaccinated at birth. In addition, contingency planning led to the procurement of a different BCG strain in 2016 (Danish strain, Serum Statens Institute Denmark replaced by Moscow strain, Serum Institute of India).

The number of children admitted to the paediatric neurology ward at Western Cape's Tygerberg Hospital, a large academic referral hospital, for diagnostic evaluation and management of tuberculous meningitis or tuberculomas showed an alarming increase during 2017 (figure). We reviewed hospital discharge summaries for these children to extract age and BCG vaccination status. Ethics approval was granted by Stellenbosch University Health Research Ethics Committee (numbers N11/01/006 and N16/11/142 to Regan Solomons). Unfortunately, BCG vaccination status was not recorded for the majority. We used Poisson regression to model the count of admissions for 10 years and estimated a specific incidence rate ratio (IRR) for 2017 compared to the preceding 3 years (2014–16),

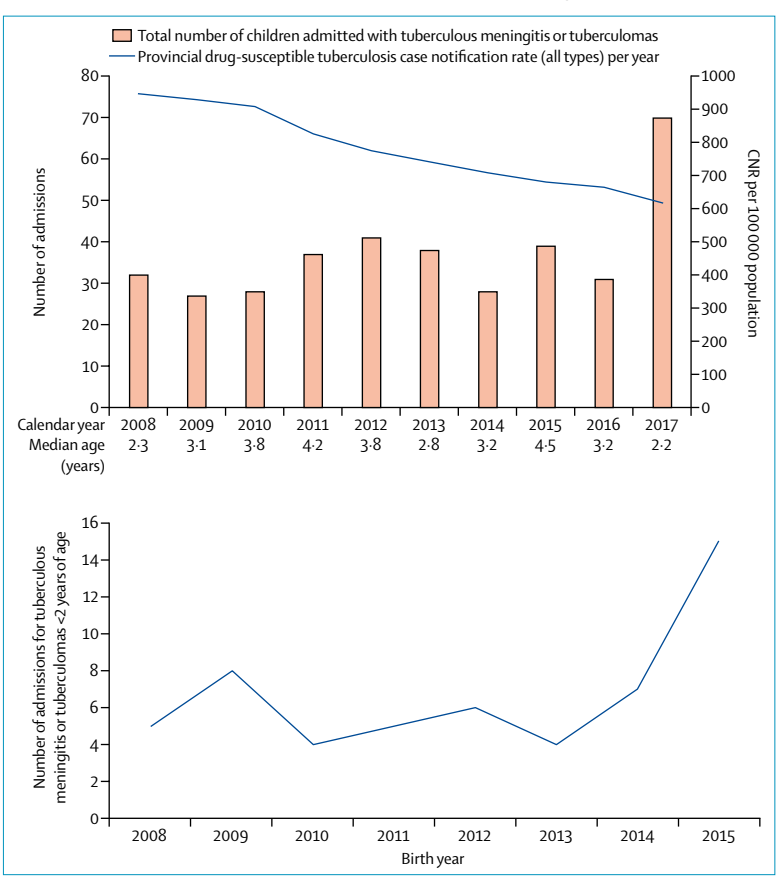

Figure: **Annual case load (top) and birth cohort analysis (bottom) of children admitted with tuberculous meningitis or tuberculomas to the paediatric neurology ward at Tygerberg Hospital, Cape Town, South Africa over a 10-year period**
Date of birth/age at admission not available for five children. CNR=case notification rate.

assuming a stable population at risk for these 4 years. The number of admissions for tuberculous meningitis or tuberculomas increased from a mean of 32·7 in 2014–16 to 70 in 2017 (IRR 2·2, 95% CI 1·6–2·9; p<0·0001). This increase cannot be explained by a concomitant increase in overall tuberculosis incidence, since the tuberculosis case notification rate in the province has been steadily declining since 2008 (figure; personal communication: Alvera Swartz, Western Cape Department of Health).[10] There were also no changes in the diagnostic algorithm used for tuberculous meningitis in this clinical setting over the 10 years of investigation, no changes in clinical care or hospital referral pathways during 2014–17, and no increase in the total number of general and specialised paediatric admissions at Tygerberg Hospital during 2017 (15 695 in 2017 *vs* a mean of 16 727 in 2014–16[11]).

We hypothesise that this sharp increase in the number of children with tuberculous meningitis is related to BCG shortages. To further evaluate the relation between BCG vaccination and tuberculous meningitis incidence, we completed birth cohort analyses. As surveillance data were only available until 2017, children were divided into birth cohorts by calendar year of birth (2008–15), with 2 years of follow-up time in each cohort (figure). Admissions for tuberculous meningitis or tuberculomas before the age of 2 years were almost three times higher in children born in 2015 compared to the mean number of those born in 2012–14 (n=15 *vs* n=5·7; IRR=2·7, 95% CI 1·3–5·5; p=0·005). Given that the median age of children with tuberculous meningitis in a large observational cohort over a period of 20 years at Tygerberg Hospital was 2·3 years,[12] it would be expected that the peak would occur just over 2 years after the actual BCG shortage occurred if shortages of BCG led to increased numbers of tuberculous meningitis cases. This was indeed the case. The median age of children with tuberculous meningitis in 2017 (2·2 years) was the lowest observed over the past 10 years (figure), further supporting this hypothesis.

These data serve as a stark warning that neonatal BCG vaccination remains a crucial component of tuberculosis control in children. Disruptions to vaccine supply can have multiple effects on the health system delivery of BCG. Strategies should be put in place to prevent such stockouts. Surveillance data on tuberculous meningitis from other settings affected by BCG shortages should be systematically collected and reported to investigate whether similar trends have been observed elsewhere. Given the paucity of current tools to combat this devastating form of tuberculosis in children, we, as a global community, must demand that supplies and quality of BCG vaccine remain secure.

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1 World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organization, 2017.

2 Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006; **367:** 1173–80.

3 Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. *Health Technol Assess* 2013; **17:** 1–372.

4 Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; **14:** 947–57.

5 World Health Organization. BCG vaccines: WHO position paper. February 2018. *Wkly Epidemiol Rec* 2018; **93:** 73–96.

6 UNICEF Supply Division. Bacillus Calmette-Guérin (BCG) vaccine supply & demand update, September 2013. https://www.unicef.org/supply/files/BCG_Supply_Status_Sept_2013.pdf (accessed June 28, 2018).

7 Marais BJ, Seddon JA, Detjen AK, et al. Interrupted BCG vaccination is a major threat to global child health. *Lancet Respir Med* 2016; **4:** 251–53.

8 Harris RC, Dodd PJ, White RG. The potential impact of BCG vaccine supply shortages on global paediatric tuberculosis mortality. *BMC Med* 2016; **14:** 138.

9 Statistics South Africa. Statistical release P0305—recorded live births, 2017. Pretoria: Statistics South Africa, 2018.

10 Massyn N, Peer N, English R, Padarath A, Barron P, Day C. District Health Barometer 2015/16. Durban: Health Systems Trust, 2016.

11 Western Cape Government. Annual report 2017: Tygerberg Hospital (in press).

12 van Well GT, Paes BF, Terwee CB, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the Western Cape of South Africa. *Pediatrics* 2009; **123:** e1–8.